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## Supplementary appendix

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**Appendix for**

# Neutralising antibodies after COVID-19 vaccination in UK haemodialysis patients

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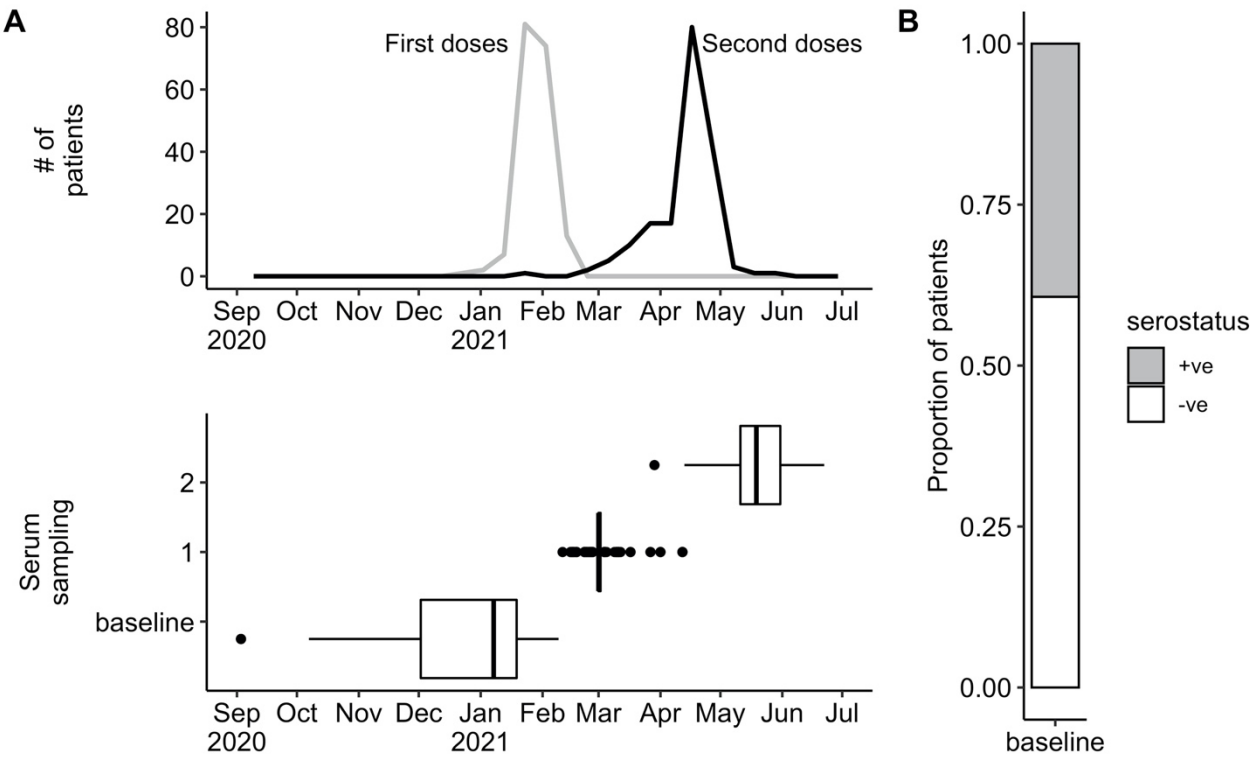



Figure 1: Study design and defining seronaive patients

(A) Study design. Dates of vaccine administration and serum sampling times are shown in the top and bottom panels respectively. N=178 in-centre haemodialysis (IC-HD) patients. Demographics are shown in Supplementary Table 1.

(B) The proportion of patients defined as seronaive at the time of first vaccination. Seronaive [serostatus -ve] was defined as (i) no detectable anti-S IgG by ELISA (143 patients of 178 had no anti-S IgG), no positive PCR results before first dose (134 patients of 143) and no detectable neutralising antibodies to either wildtype SARS-CoV-2 or SARS-CoV-2 carrying the D614G spike mutation at baseline (108 patients of 134). Seronaive demographics are shown in Supplementary Table 2.

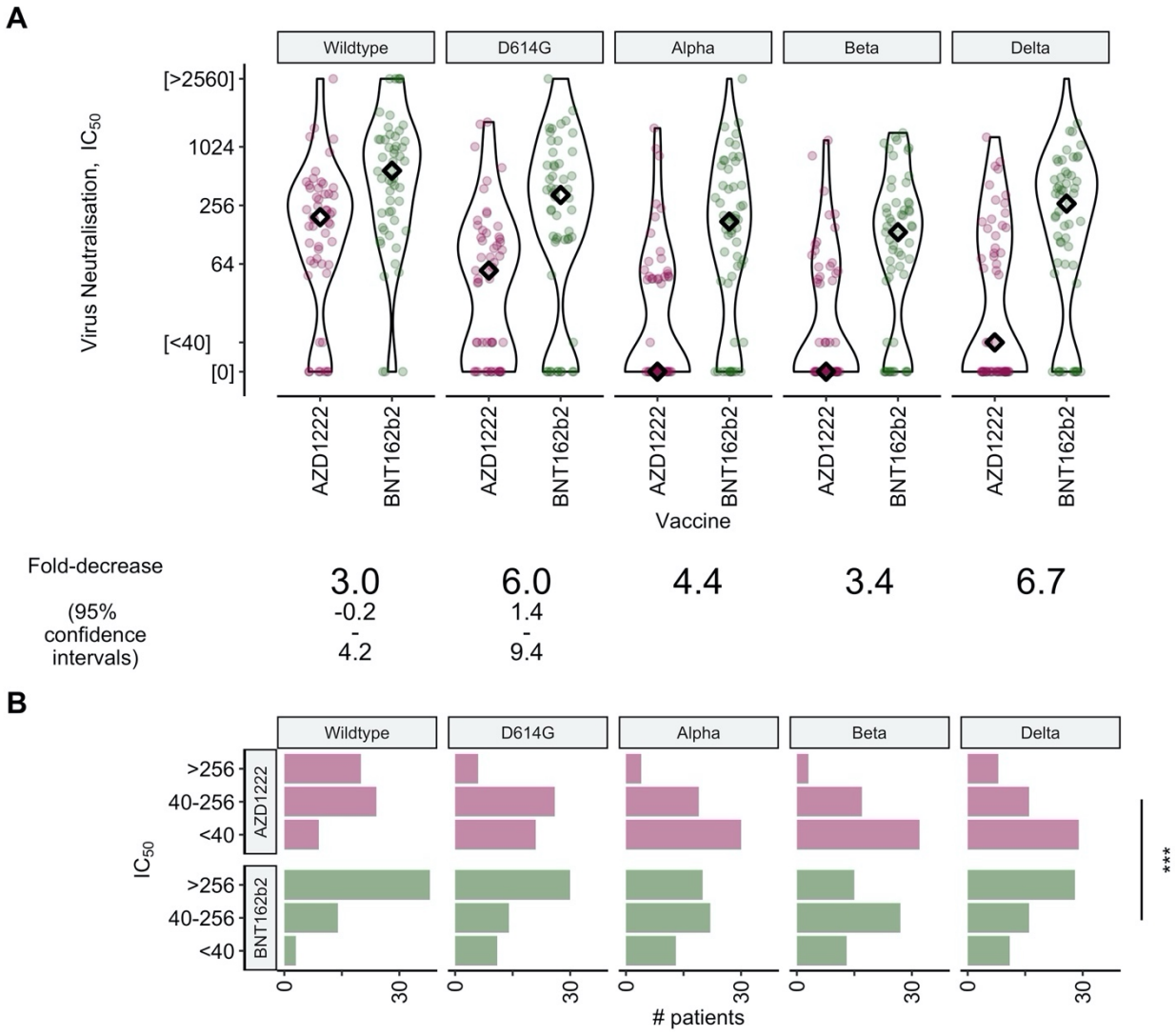



Figure 2: Neutralising antibody responses after two doses of AZD1222 or BNT162b2 in seronaive haemodialysis patients

(A) Live virus microneutralisation titres against SARS-CoV-2: wildtype, the D614G spike mutant, and VOCs - Alpha, Beta and Delta - 33 days after two doses in seronaive haemodialysis patients comparing AZD1222 and BNT162b2 responses (AZD1222 n=53, BNT162b2 n=55).
(B) Data as in (A) plotted with stratification of titres into three categories. An ordered logistic regression model: IC50_binned ~ variant * vaccine was fitted. ANOVA P<0.0001 is indicated by *** for the vaccine term (see also Supplementary Table 3 for ordered logistic regression).

In (A), the medians are plotted as a black diamond. Note that the median is below the quantitative range ($IC_{50}$<40) in some instances. The estimated fold-decrease between AZD1222 and BNT162b2 is shown in (A), where the AZD1222 median $IC_{50}$<40, it was assigned a value of 40 for a conservative estimate of fold-decrease, and no confidence intervals are calculated.

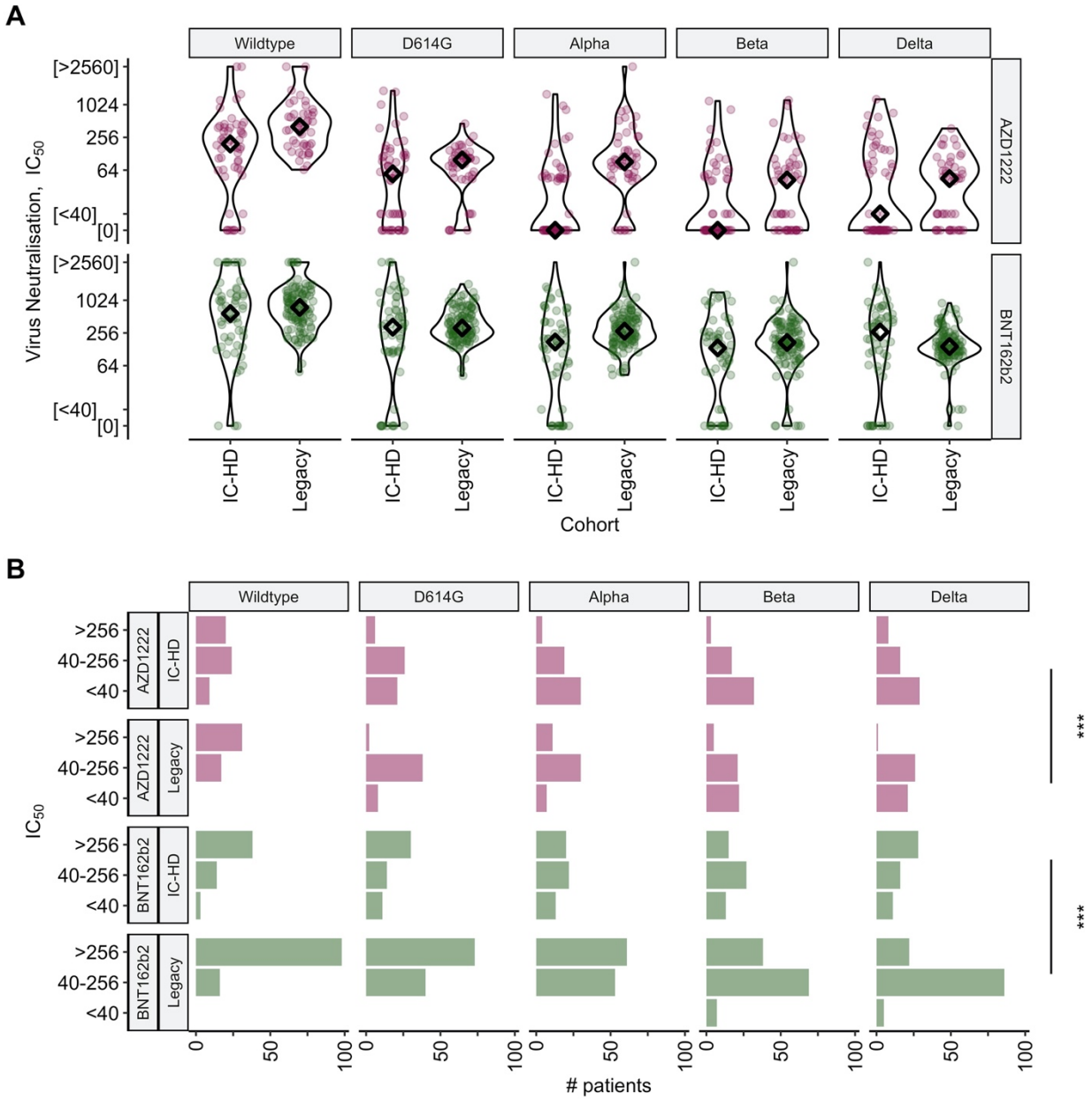



Figure 3: Neutralising antibody responses after two doses of AZD1222 or BNT162b2 in seronaive haemodialysis patients compared to never-symptomatic healthy individuals

(A) Microneutralisation titres, comparing two doses in seronaive haemodialysis patients (IC-HD) with two doses in never-symptomatic healthy individuals (Legacy) for AZD1222 and BNT162b2. Legacy demographics are shown in Supplementary Table 4.

(B) Data as in (A) stratified into three bins of neutralizing antibody. An ordered logistic regression model: IC50_binned ~ variant * cohort was fitted for each vaccine separated. ANOVA P<0.0001 is indicated by *** for the cohort term (see also Supplementary Tables 5-6 for ordered logistic regression).

In (A), the medians are plotted as a black diamond. Note that the median is below the quantitative range ($IC_{50}$<40) in some instances.

# Supplementary tables 1-7

*Supplementary table 1: Demographics of the whole interim report cohort, grouped by vaccine*

| | AZD1222 | BNT162B2 | P-VALUE |
|---|---|---|---|
| | n = 94 | n = 84 | |
| **AGE** | | | **0.946** |
| | 63.2 (13.5) | 63.1 (13.3) | |
| **GENDER** | | | **0.685** |
| **F** | 32 (34%) | 32 (38.1%) | |
| **M** | 62 (66%) | 52 (61.9%) | |
| **ETHNICITY** | | | **0.139** |
| | 0 (0%) | 0 (0%) | |
| **ASIAN** | 37 (39.4%) | 38 (45.2%) | |
| **BLACK** | 20 (21.3%) | 7 (8.3%) | |
| **MIXED** | 0 (0%) | 1 (1.2%) | |
| **OTHER** | 4 (4.3%) | 3 (3.6%) | |
| **WHITE** | 33 (35.1%) | 35 (41.7%) | |
| **DIABETIC** | | | **0.921** |
| **N** | 51 (54.3%) | 44 (52.4%) | |
| **Y** | 43 (45.7%) | 40 (47.6%) | |
| **IMMUNOSUPPRESSED** | | | **0.133** |
| **N** | 78 (83%) | 77 (91.7%) | |
| **Y** | 16 (17%) | 7 (8.3%) | |
| **DIALYSIS CENTRE CODE** | | | **<.001** |
| **A** | 19 (20.2%) | 1 (1.2%) | |
| **B** | 58 (61.7%) | 15 (17.9%) | |
| **C** | 17 (18.1%) | 68 (81%) | |

*Supplementary table 2: Demographics of the seronaive cohort*

| | AZD1222 | BNT162B2 | P-VALUE |
|---|---|---|---|
| | n = 53 | n = 55 | |
| **AGE** | | | **0.792** |
| | 63.3 (13.9) | 63.9 (12.1) | |
| **GENDER** | | | **1** |
| **F** | 20 (37.7%) | 20 (36.4%) | |
| **M** | 33 (62.3%) | 35 (63.6%) | |
| **ETHNICITY** | | | **0.244** |
| | 0 (0%) | 0 (0%) | |
| **ASIAN** | 17 (32.1%) | 24 (43.6%) | |
| **BLACK** | 11 (20.8%) | 4 (7.3%) | |
| **MIXED** | 0 (0%) | 1 (1.8%) | |
| **OTHER** | 1 (1.9%) | 1 (1.8%) | |
| **WHITE** | 24 (45.3%) | 25 (45.5%) | |
| **DIABETIC** | | | **1** |
| **N** | 28 (52.8%) | 30 (54.5%) | |
| **Y** | 25 (47.2%) | 25 (45.5%) | |
| **IMMUNOSUPPRESSED** | | | **0.357** |
| **N** | 43 (81.1%) | 52 (94.5%) | |
| **Y** | 10 (18.9%) | 3 (3.5%) | |
| **DIALYSIS CENTRE CODE** | | | **<.001** |
| **A** | 10 (18.9%) | 0 (0%) | |
| **B** | 31 (58.5%) | 7 (12.7%) | |
| **C** | 12 (22.6%) | 48 (87.3%) | |

For supplementary tables 1 and 2, P values are t tests for single level continuous variables (e.g. age), ANOVAs for higher levels (e.g. ethnicity) and $\chi^2$ tests for categorical data (e.g. gender). Apart from dialysis centre, the cohorts of AZD1222 and BNT162b2 are matched for age, gender ethnicity, diabetes and immunosuppressed status.

*Supplementary table 3: Ordered logistic regression model of effect of variant and vaccine type on neutralising antibody titres 33 days after 2 doses in seronaive IC-HD patients, relating to Figure 2B. Model: ic50_binned ~ variant * vaccine*

| FACTOR | *COEF* | *SE* | *WALD Z* | *PR(>\|Z\|)* |
|---|---|---|---|---|
| **VARIANT (VS WILDTYPE)** | | | | |
| **D614G** | -1.1689 | 0.3587 | -3.26 | 0.0011 |
| **ALPHA** | -1.7515 | 0.3731 | -4.69 | <0.0001 |
| **BETA** | -1.9525 | 0.3812 | -5.12 | <0.0001 |
| **DELTA** | -1.5595 | 0.3745 | -4.16 | <0.0001 |
| **VACCINE (VS AZD1222)** | 1.2487 | 0.3844 | 3.25 | 0.0012 |
| **BNT162B2** | -1.7515 | 0.3731 | -4.69 | <0.0001 |
| **INTERACTION (VARIANT * VACCINE)** | | | | |
| **D614G * BNT162B2** | 0.3755 | 0.5316 | 0.71 | 0.4801 |
| **ALPHA * BNT162B2** | 0.321 | 0.5318 | 0.6 | 0.5462 |
| **BETA * BNT162B2** | 0.2872 | 0.5332 | 0.54 | 0.5902 |
| **DELTA * BNT162B2** | 0.6437 | 0.5395 | 1.19 | 0.2328 |

**ANOVA**

Wald Statistics Response: ic50_binned

| FACTOR | COEF | SE | WALD Z |
|---|---|---|---|
| **VARIANT (INCL. HIGHER ORDER FACTORS)** | 55.27 | 8 | <0.0001 |
| **VACCINE (INCL. HIGHER ORDER FACTORS)** | 81.8 | 5 | <0.0001 |
| **INTERACTION** | 1.45 | 4 | 0.8351 |

*Supplementary table 4: Demographics comparison between IC-HD and Legacy cohorts*

| | IC-HD | LEGACY | P-VALUE |
|---|---|---|---|
| | n = 108 | n = 162 | |
| **AGE** | | | **<.001** |
| | 63.6 (13.9) | 40.5 (11.4) | |
| **GENDER** | | | **<.001** |
| **F** | 40 (37%) | 102 (63%) | |
| **M** | 68 (63%) | 60 (37%) | |

*Supplementary table 5: Ordered logistic regression model of effect of variant and vaccine type on neutralising antibody titres after 2 doses of AZD1222 in seronaive IC-HD patients or Legacy participants, relating to Figure 3B. Model: ic50_binned ~ variant * cohort*

**AZD1222 recipients**

| FACTOR | COEF | SE | WALD Z | PR(>\|Z\|) |
|---|---|---|---|---|
| **VARIANT (VS WILDTYPE)** | | | | |
| **D614G** | -1.5474 | 0.3934 | -3.93 | <0.0001 |
| **ALPHA** | -2.2325 | 0.4032 | -5.54 | <0.0001 |
| **BETA** | -2.4547 | 0.4099 | -5.99 | <0.0001 |
| **DELTA** | -2.0145 | 0.4061 | -4.96 | <0.0001 |
| **COHORT (VS IC-HD)** | 1.3244 | 0.4055 | 3.27 | 0.0011 |
| **LEGACY** | -1.5474 | 0.3934 | -3.93 | <0.0001 |
| **INTERACTION (VARIANT * COHORT)** | | | | |
| **D614G * LEGACY** | -0.7819 | 0.5519 | -1.42 | 0.1566 |
| **ALPHA * LEGACY** | 0.4837 | 0.5645 | 0.86 | 0.3915 |
| **BETA * LEGACY** | -0.6531 | 0.569 | -1.15 | 0.251 |
| **DELTA * LEGACY** | -1.1898 | 0.5631 | -2.11 | 0.0346 |

**ANOVA**

Wald Statistics Response: ic50_binned

| FACTOR | COEF | SE | WALD Z |
|---|---|---|---|
| **VARIANT (INCL. HIGHER ORDER FACTORS)** | 104.57 | 8 | <0.0001 |
| **COHORT (INCL. HIGHER ORDER FACTORS)** | 35.13 | 5 | <0.0001 |
| **INTERACTION** | 11.31 | 4 | 0.0233 |

*Supplementary table 6: Ordered logistic regression model of effect of variant and vaccine type on neutralising antibody titres after 2 doses of BNT162b2 in seronaive IC-HD patients or Legacy participants, relating to Figure 3B. Model: ic50_binned ~ variant * cohort*

**BNT162b2 recipients**

| FACTOR | COEF | SE | WALD Z | PR(>\|Z\|) |
|---|---|---|---|---|
| **VARIANT (VS WILDTYPE)** | | | | |
| **D614G** | -0.8896 | 0.4069 | -2.19 | 0.0288 |
| **ALPHA** | -1.7099 | 0.4081 | -4.19 | <0.0001 |
| **BETA** | -2.0401 | 0.4066 | -5.02 | <0.0001 |
| **DELTA** | -1.0378 | 0.4056 | -2.56 | 0.0105 |
| **COHORT (VS IC-HD)** | 1.0603 | 0.3972 | 2.67 | 0.0076 |
| **LEGACY** | -0.8896 | 0.4069 | -2.19 | 0.0288 |
| **INTERACTION (VARIANT * COHORT)** | | | | |
| **D614G * LEGACY** | -0.2846 | 0.5249 | -0.54 | 0.5877 |
| **ALPHA * LEGACY** | 0.1135 | 0.5207 | 0.22 | 0.8275 |
| **BETA * LEGACY** | -0.3623 | 0.5169 | -0.7 | 0.4834 |
| **DELTA * LEGACY** | -1.7592 | 0.5183 | -3.39 | 0.0007 |

**ANOVA**

Wald Statistics Response: ic50_binned

| FACTOR | COEF | SE | WALD Z |
|---|---|---|---|
| **VARIANT (INCL. HIGHER ORDER FACTORS)** | 123.77 | 8 | <0.0001 |
| **COHORT (INCL. HIGHER ORDER FACTORS)** | 32.72 | 5 | <0.0001 |
| **INTERACTION** | 19.6 | 4 | 6.00E-04 |

Whilst there is a significant cohort effect, there is also (unlike for AZD1222) an opposing interaction effect is seen with Delta, such that the two cohorts have equivalent Delta responses.

*Supplementary table 7: Ordered logistic regression model of effect of variant and vaccine type on neutralising antibody titres after 2 doses of either vaccine in seropositive IC-HD patients, relating to Supplementary Figure 1. Model: ic50_binned ~ variant * vaccine*

**SEROPOSTIVE (at baseline) patients**

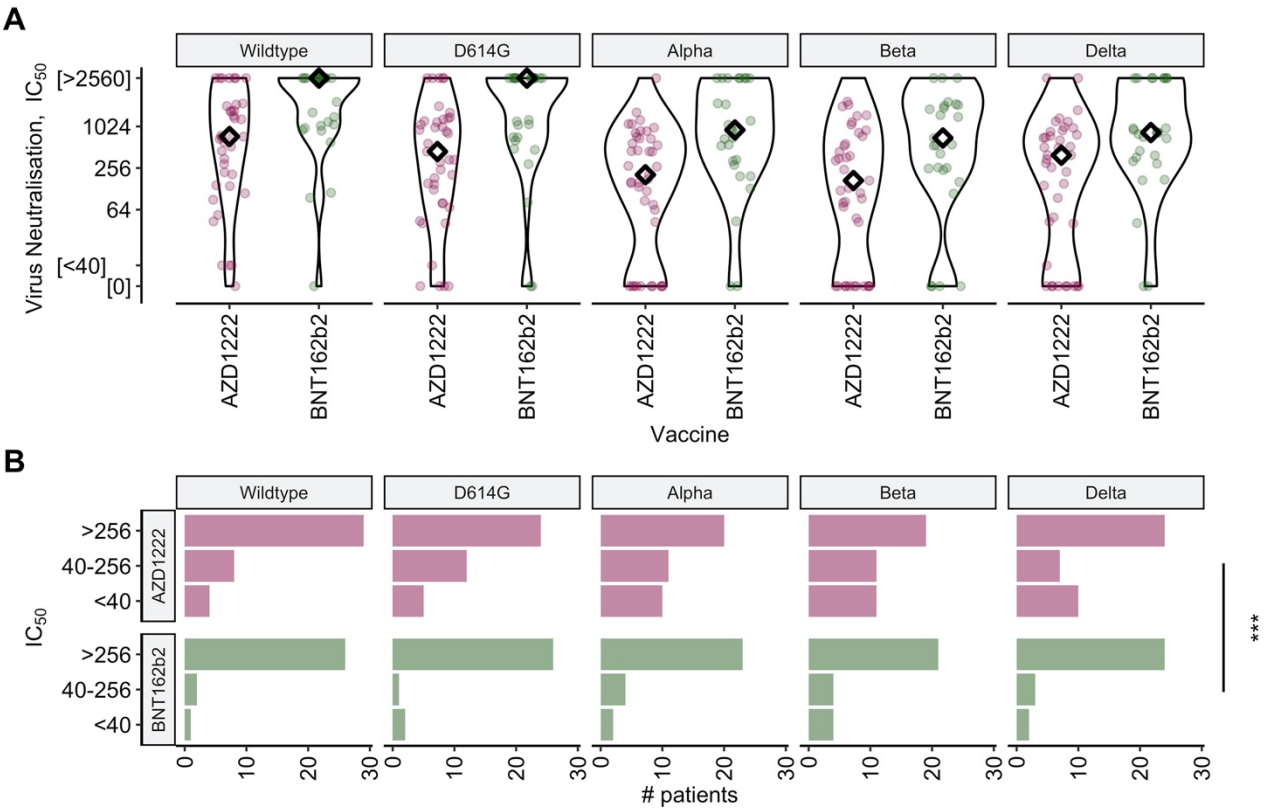
| FACTOR | COEF | SE | WALD Z | PR(>\|Z\|) |
|---|---|---|---|---|
| **VARIANT (VS WILDTYPE)** | | | | |
| **D614G** | -0.4671 | 0.4525 | -1.03 | 0.302 |
| **ALPHA** | -0.9416 | 0.4472 | -2.11 | 0.0352 |
| **BETA** | -1.0489 | 0.4464 | -2.35 | 0.0188 |
| **DELTA** | -0.6607 | 0.4588 | -1.44 | 0.1498 |
| **VACCINE (VS AZD1222)** | 1.2509 | 0.6961 | 1.8 | 0.0723 |
| **BNT162B2** | -0.4671 | 0.4525 | -1.03 | 0.302 |
| **INTERACTION (VARIANT * VACCINE)** | | | | |
| **D614G * BNT162B2** | 0.428 | 0.9735 | 0.44 | 0.6602 |
| **ALPHA * BNT162B2** | 0.1352 | 0.8817 | 0.15 | 0.8782 |
| **BETA * BNT162B2** | -0.1859 | 0.8598 | -0.22 | 0.8288 |
| **DELTA * BNT162B2** | 0.0612 | 0.9061 | 0.07 | 0.9461 |

**ANOVA**

Wald Statistics Response: ic50_binned

| FACTOR | COEF | SE | WALD Z |
|---|---|---|---|
| **VARIANT (INCL. HIGHER ORDER FACTORS)** | 11.16 | 8 | 0.1930 |
| **VACCINE (INCL. HIGHER ORDER FACTORS)** | 25.20 | 5 | <0.0001 |
| **INTERACTION** | 0.56 | 4 | 0.9678 |

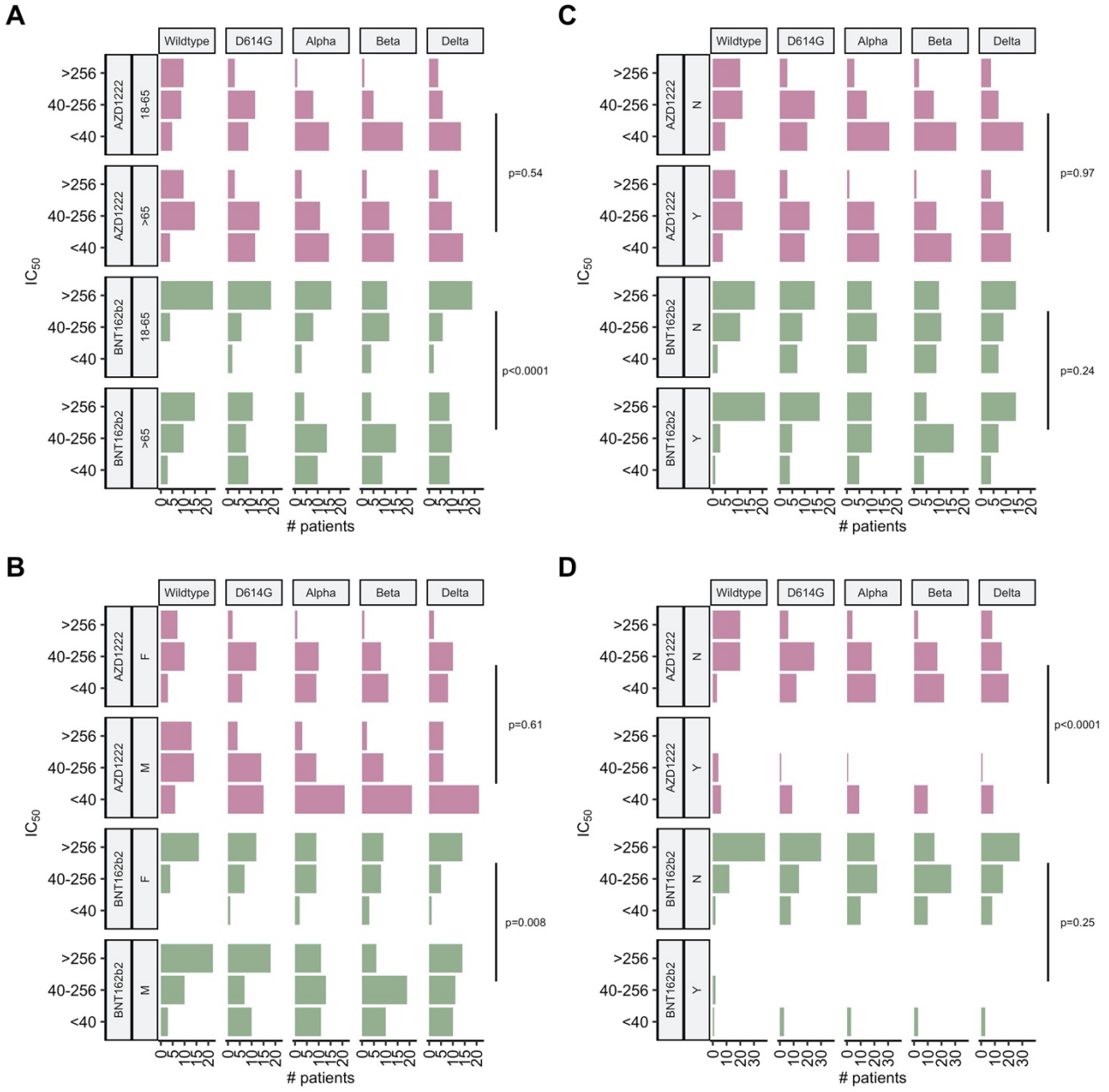
# Supplementary figure 1: Live-virus microneutralisation antibody titres in infection-experienced IC-HD patients




(A) Live virus microneutralisation titres against SARS-CoV-2: wildtype, the D614G spike mutant, and VOCs - Alpha, beta and Delta - 33 days after two doses in infection-experienced haemodialysis patients comparing AZD1222 and BNT162b2 responses (70 patients in total (AZD1222 n=41; BNT162b2 n=29).

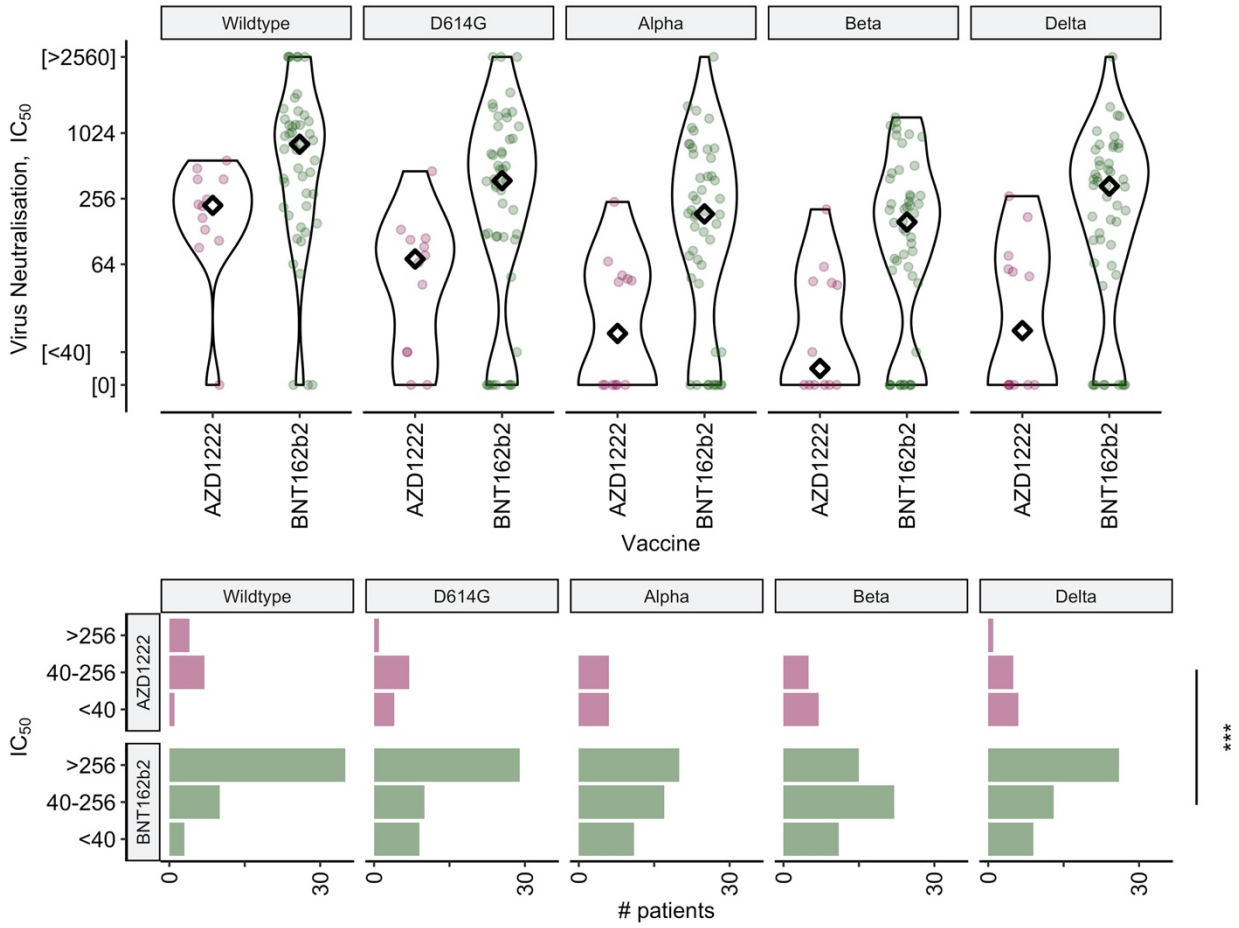
(B) Data as in (A) plotted with stratification of titres, P < 0.0001 from denoted by *** (ANOVA of regression model; see also Supplementary Table 7 for ordered logistic regression).

# Supplementary figure 2: Comparing nAbT responses by age group, gender, diabetes and immunosuppression in seronaive IC-HD patients




NAbTs are compared at a median of 33 days after two doses in seronaive haemodialysis patients. The data is grouped by age (18-65 or >65 years old, A), gender (B), the presence of diabetes (C), or the presence of immunosuppression (D) and each vaccine is shown separately. *P* values from ANOVA for the effect of age (AZD1222 *P*=0.54, BNT162b2 *P*<0.0001), gender (*P*=0.61, *P*=0.008), diabetes (*P*=0.97, *P*=0.24), or immunosuppression (*P*<0.0001, *P*=0.25), performed on ordinal linear regression models are provided. (AZD1222 model: ic50_binned ~ age * variant, BNT162b2 model: ic50_binned ~ age * variant, with the variable 'age' changed for each panel to gender, diabetes or immunosuppression as indicated).

# Supplementary figure 3: Comparing nAbT between AZD1222 and BNT162b2 in a single HD centre in seronaive IC-HD patients




(A) Live virus microneutralisation titres against SARS-CoV-2: wildtype, the D614G spike mutant, and VOCs – Alpha, Beta and Delta – after two doses in seronaive haemodialysis patients comparing AZD1222 and BNT162b2 responses in a single centre (AZD1222 n=12, BNT162b2 n=48).

(B) Data as in (A) plotted with stratification of titres into three categories. An ordered logistic regression model: IC50_binned ~ variant * vaccine was fitted. ANOVA P<0.001 is indicated by *** for the vaccine term.

## Methods

### *Study objectives and design*

We are performing a cohort study of 1,200 IC-HD patients across the UK. The study has several objectives:

1. Confirm the immunogenicity of BNT162b2 and AZD1222 in IC-HD patients, including the generation of neutralising antibodies.
    a. Confirm augmentation of the antibody response with the second dose of vaccine
    b. Assess the longevity of the antibody response, including neutralising antibody.
2. Compare the profiles of neutralising antibodies generated between BNT162b2 and AZD1222 IC-HD recipients.
3. Compare the profiles of neutralising antibodies generated by either vaccine between different age groups, different genders, different ethnicities, and different primary renal diseases.
4. Compare the profiles of neutralising antibodies generated between patients with and without diabetes or with and without immunosuppression.
5. Exploratory / discovery phase, where novel patterns / correlations are identified to provide hypothesis for testing in other cohorts / specifically targeted studies.

For any cohort comparison we expect, given the nature of the UK's IC-HD population (its ethnicities, age, gender and the frequencies of diabetes and immunosuppression) to be able to assemble groups of >100 patients for each comparison.

We planned serum collections before vaccination, 28 days after each vaccination, and 6 & 12 months after commencing vaccination.

### *Clinical cohorts*

Three haemodialysis centres are included in this interim report, and one healthy control cohort. In-centre haemodialysis patients were included if they were able to consent into their local study and were clinically eligible to receive the available vaccine. Home haemodialysis patients and peritoneal dialysis patients were not included. The data shown is censored for individuals who received two doses of vaccine, and had available neutralising antibody titres at the first three study time points (baseline, ~ 28 days after vaccine 1, and ~ 33 days after vaccine 2). Anonymised (coded only against a research identifier) sera and phenotype data were provided for central analysis: age, gender, ethnicity, diabetes, immunosuppression, primary renal disease, alongside the dates of vaccine, vaccine manufacturer and the dates of serum sampling. Ethnicity was recorded as Asian, Black, Mixed, White or Other (in line with UK government advice at the time of commencing the study *https://webarchive.nationalarchives.gov.uk/20210224165417/https://design-system.service.gov.uk/patterns/ethnic-group/* ). Diabetes was recorded as Y/N, and we

defined immunosuppression as Y/N as in Billany et al. (1). Individuals were vaccinated intramuscularly as part of their usual care, with either 0.5mL [not less than $2.5x10^8$ infectious units] AZD-1222, ChAdOx1-S (Oxford-AstraZeneca) or 30ug BNT162b2 (Pfizer-BioNTech), at the interval indicated in Figure 1.

*Leicester cohort (IC-HD)*
Patient samples were collected as part of the study “PHENOTYPING SEROCONVERSION FOLLOWING VACCINATION AGAINST COVID-19 IN PATIENTS ON HAEMODIALYSIS”, with REC approval from West Midlands - Solihull Research Ethics Committee (REC: 21/WM/0031) sponsored by the University of Leicester and included consent for samples to transfer to the Francis Crick Institute. This work was conducted locally with support from the NIHR Leicester Biomedical Research Centre and funding from the Leicester Hospitals Charity, University Hospitals of Leicester NHS Trust. Data from these patients have been published previously (1).

*Royal Free Hospital cohort (IC-HD)*
Patients were consented to join the UCL-RFH biobank approved study "ANALYSIS OF ANTI-SARS COV2 IMMUNE RESPONSE". The UCL-RFH Biobank has been given a favourable ethics opinion for conduct in the NHS by the Wales research ethics Committee 4 (REC: 16/WA/0289). This work was conducted locally with funding support from The St Peter’s Trust, Royal Free Charity.

*Oxford cohort (IC-HD)*
Patients were consented to join the Oxford Radcliffe Biobank approved study “Immunological responses to COVID-19 vaccines in transplant and haemodialysis patients” (ref: ORB 21/A014). The Oxford Radcliffe Biobank has a favourable ethics opinion from the South Central Oxford Committee C (REC: 19/SC/0173). This work was conducted locally with funding support by the Oxford Transplant Foundation and the Oxfordshire Health Services Research Committee, part of Oxford Hospitals Charity.

*Legacy cohort (Healthy volunteers)*
The Legacy cohort (NCT04750356) has been described recently (2,3). It comprises of healthcare workers from University College London Hospital and scientists from the Francis Crick Institute, London. The Legacy study was approved by London Camden and Kings Cross Health Research Authority (HRA) Research and Ethics committee (REC: 20/HRA/4717) and sponsored by University College London. The full dataset was kindly made available by the Legacy team for analysis in this report. Please see Wall et al. for access details (2,3).

***Serological Analysis and live-virus neutralisation***
All serum samples were collected during routine IC-HD sessions from the HD circuit, without additional venepuncture. Sera were separated from blood in local laboratories and stored frozen. Sera were shipped to the Crick on dry ice, and barcoded whilst frozen. All serological analyses, including in-house anti-Spike IgG ELISA and live-virus microneutralisation were performed as described previously (4).

### *Data analysis, statistics*

Data analysis was performed in R/Rstudio, using Rmarkdown. Anonymised data wrangling used a mix of base R and tidyverse. Demographics were compared using t-tests, ANOVAs or $\chi^2$ tests as indicated. As previously (2,3), $IC_{50}$ values above the quantitative limit of detection of the assay (>2560) were re-coded as 5120; $IC_{50}$ values below the quantitative limit of the assay (< 40) but within the qualitative range were re-coded as 10 and data below the qualitative range (i.e. no response observed) were re-coded as 5. $IC_{50}$ values are shown on a log2 scale throughout. 95% confidence intervals of the fold changes of median NAbT were estimated using *bootstrap* and *boot.ci*, with *type="basic"* argument, which does not assume normality. Where the median is below the quantitative range of the assay and estimated effect is shown using the lower bound of the quantitative range ($IC_{50}$=40), and confidence intervals are not reported. Stratified $IC_{50}$ NAbT were compared using ordered logistic regression, from the rms package, using the model: $IC_{50}$ binned ~ variant * vaccine, or $IC_{50}$ binned ~ variant * cohort to compare AZD1222 Legacy with IC-HD recipients, and BNT162b2 Legacy with IC-HD recipients. The ordinal regression was necessary due to non-random censoring of the IC50s at low levels of response (a fully parametric model would be biased, and a dichotomisation into responders/non-responders is less powerful). Plots were generated using ggplot2 and ggpubr packages.

### *Data Sharing*

All R code to reproduce all figures and analyses is freely available at (https://github.com/EdjCarr/Crick-HD-AZD-BNT-VOCs-2021-07/). The public dataset omits dialysis centre, age and dates, to ensure no individual participant is unique. The Legacy data are already available as outlined in their original publications (2,3).

### *Ethics*

This work is covered by the following REC approvals: REC: 21/WM/0031, REC: 16/WA/0289, REC: 19/SC/0173, REC: 20/HRA/4717, as described in the cohort descriptions above. Within REC: 21/WM/0031, central processing in the Crick was included.

### *Role of the funding source*

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The corresponding authors had full access to all the data and the final responsibility to submit for publication.

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